

10/055,502

* * * * * STN Columbus * * * * *

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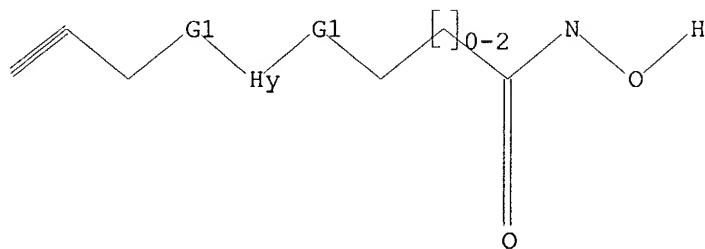
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G1 C,O,S,N

Structure attributes must be viewed using STN Express query preparation.

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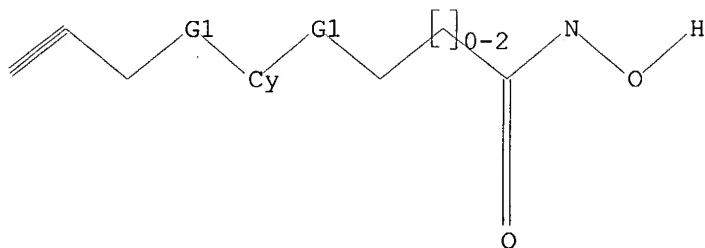
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L4 HAS NO ANSWERS

L4 STR



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Structure attributes must be viewed using STN Express query preparation.

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L6 135 SEA SSS FUL L4

10/055,502

=> file ca

=> s 16

L7 3 L6

=> d ibib abs fhitr 1-3

L7 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 136:118280 CA

TITLE: Preparation of N-hydroxy[(alkynyloxy)phenylsulfanyl]alkanoamides and analogs as TACE and MMP inhibitors

INVENTOR(S): Levin, Jeremy I.; Venkatesan, Aranapakam M.; Cole, Derek C.; Chen, James M.; Davis, Jamie M.; Grosu, George T.

PATENT ASSIGNEE(S): American Cyanamid Company, USA

SOURCE: U.S., 43 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 6340691 | B1 | 20020122 | US 2000-492977 | 20000127 |
| US 2002147342 | A1 | 20021010 | US 2001-55502 | 20011113 |
| PRIORITY APPLN. INFO.: | | | US 1999-160085P | P 19990127 |
| | | | US 2000-492977 | A3 20000127 |

OTHER SOURCE(S): MARPAT 136:118280

AB R1C.tplbond.CCR2R3Z1Z2Z3CR8R9ZCON(OH)R12 [I; R1 = H, alkyl, (hetero)aryl, etc.; R2,R3 = H, cyano, alkyl, CCH (sic); R8,R9 = H, aryl(alkyl), heteroaryl, etc.; R12 = H, heterocyclyl, (hetero)aryl, etc.; Z = bond, (un)substituted CH2, -CH2CH2; Z1 = O, SO0-2, (un)substituted NH, C (sic); Z2 = (hetero)arylene; Z3 = O, SO0-2, (un)substituted NH, CH (sic)] were prepd. Thus, MeCHBrCO2Et was thioetherified by 4-(HO)C6H4SH and the product etherified by MeC.tplbond.CCH2Br to give, in 2 addnl. steps, 4-(MeC.tplbond.CCH2O)C6H4SCHMeCONHOH. Data for biol. activity of I were given.

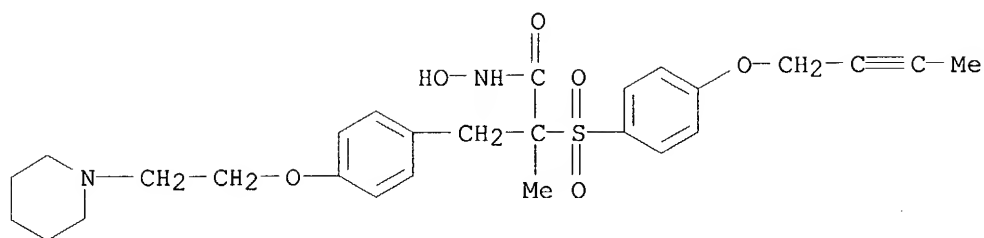
IT 287391-43-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-hydroxy[(alkynyloxy)phenylsulfanyl]alkanoamides and analogs as TACE and MMP inhibitors)

RN 287391-43-9 CA

CN Benzenepropanamide, .alpha.-[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy-.alpha.-methyl-4-[2-(1-piperidinyl)ethoxy]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 135:318704 CA

TITLE: Preparation of benzimidazole-, benzoxazole- and benzothiazolesulfonamide amino acid derivatives as selective matrix metalloproteinase inhibitors

INVENTOR(S): Park, Young-Jun; Bae, Hae-Young; Yoo, Ji-Uk; Chae, Myeong-Yun; Paek, Sang-Hyun; Min, Hye-Kyung; Park, Hyun-Gyu; Ryu, Choon-Ho; Kim, Kyung-Chul; Lee, Jeoung-Wook

PATENT ASSIGNEE(S): Samsung Electronics Co., Ltd., S. Korea

SOURCE: PCT Int. Appl., 115 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

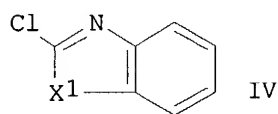
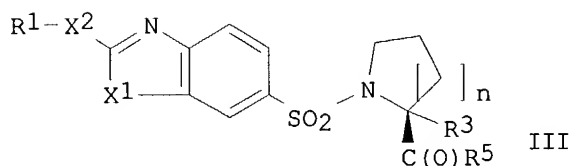
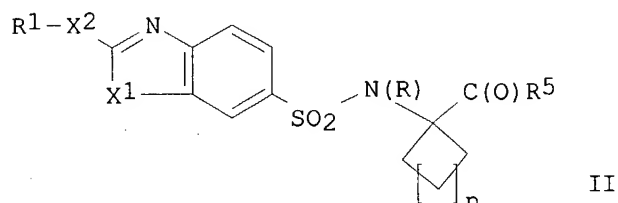
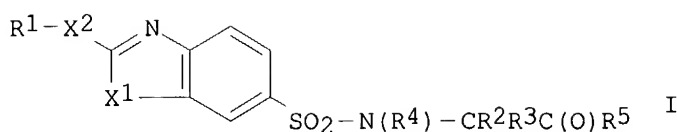
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2001077092 | A1 | 20011018 | WO 2001-KR585 | 20010407 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| AU 2001048884 | A5 | 20011023 | AU 2001-48884 | 20010407 |
| EP 1208092 | A1 | 20020529 | EP 2001-922101 | 20010407 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| JP 2003530389 | T2 | 20031014 | JP 2001-575566 | 20010407 |
| US 2002169314 | A1 | 20021114 | US 2001-18507 | 20011206 |
| US 6548667 | B2 | 20030415 | | |
| PRIORITY APPLN. INFO.: | | | KR 2000-18327 | A 20000407 |
| | | | KR 2000-18328 | A 20000407 |
| | | | KR 2000-18431 | A 20000408 |
| | | | WO 2001-KR585 | W 20010407 |

OTHER SOURCE(S): MARPAT 135:318704

GI



AB The present invention provides novel sulfonamide derivs. (I (e.g. (2R)-3-methyl-2-[(2-phenylthiobenzothiazole-6-sulfonyl)amino]butanoic acid Me ester), II (n = 0-4) and III (n = 0-4)), useful as an inhibitors of matrix metalloproteinase (MMP), its isomers, pharmaceutically acceptable salts thereof and a process for prepg. the same. Since the sulfonamide derivs. of the present invention selectively inhibit MMP activity in vitro, the MMP inhibitors comprising the sulfonamide derivs. as an effective ingredient can be practically applied for the prevention and treatment of all sorts of diseases caused by overexpression and overactivation of MMP. In I: R1 denotes H, C1-12 alkyl, carbocyclic aryl-lower alkyl, C3-7 cycloalkyl, C3-7 cycloalkyl-lower alkyl, (oxo, amino or thio) C3-7 cycloalkyl, (oxo, amino or thio) C3-7 cycloalkyl-lower alkyl, C2-12 lower alkenyl, C2-12 lower alkynyl, carbocyclic aryl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, halo lower alkyl, biaryl-lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl (thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, (N-lower alkylpiperazino, or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl. R2 denotes H, lower alkyl, carbocyclic aryl-lower alkyl, C1-4 carbocyclic aryl-lower alkyl, C1-4 heterocyclic aryl-lower alkyl, C1-5 alkoxyphenyl-lower alkyl, C1-5 alkenoxyphenyl-lower alkyl, C1-5 alkynoxyphenyl-lower alkyl, heterocyclic aryl-lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, thio-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, carboxy-lower alkyl, (amino, mono or dialkylamino) lower alkyl or acylamino lower alkyl. R3 denotes H or C1-6-lower alkyl. R4 denotes H, C1-12 alkyl, C3-7 cycloalkyl, C3-7 cycloalkyl-lower alkyl, (oxo, amino or thio) C3-7 cycloalkyl, (oxo, amino or thio) C3-7 cycloalkyl-lower alkyl, carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, biaryl-lower alkyl, halo lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl-(thio, sulfinyl or

sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, carboxy lower alkyl, (N-lower alkylpiperazino, or N-carbocyclic or heterocyclic aryl piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl. R5 denotes hydroxy, alkoxy, halogen, thiol, thioalkoxy or hydroxylamine. X1 and X2 denote N-R7 (R7 is H, C1-6-lower alkyl, aryl, heteroaryl or arylalkyl), S or O. I can be prepd. by (i) reacting a sulfonyl halide with H₂NCR₂R₃CO₂R₆ (R₆ = protecting group) in an org. solvent in the presence of a base to give a sulfonamide; (ii) replacing the H on N using R₄-L (L = reactive leaving group) in an org. solvent in the presence of a base; and (iii) hydrolyzing the intermediate to give I (R₅ = OH), or further condensing I (R₅ = OH) to prep. I (R₅ = NHOH). Alternatively, I can be prepd. by (i) chlorosulfonylating IV; (ii) reacting this intermediate with an amino acid deriv. in an org. solvent in the presence of base to give a sulfonamide; (iii) heating this intermediate and R₁-X₂H together at 70 to 80.degree. in an org. solvent in the presence of base to cause substitution for Cl; (iv) reacting this intermediate with R₄-L (L = reactive leaving group) in an org. solvent in the presence of base to cause substitution for H on N; and, (v) hydrolyzing this intermediate into I (R₅ = OH), or further condensing I (R₅ = OH) to prep. I (R₅ = NHOH). .apprx.70 Example preps. of intermediates and products are given. Inhibition rates for some of the claimed compds. are reported for gelatinase A (MMP-2), gelatinase B (MMP-9) and collagenase (MMP-1).

IT 367517-41-7P

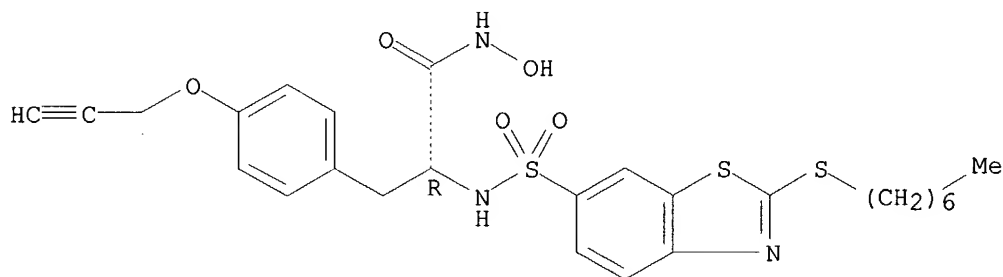
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. of benzimidazole-, benzoxazole- and benzothiazolesulfonamide amino acid derivs. as selective matrix metalloproteinase inhibitors)

RN 367517-41-7 CA

CN Benzenepropanamide, .alpha.-[[[2-(heptylthio)-6-benzothiazolyl]sulfonyl]amino]-N-hydroxy-4-(2-propynyloxy)-, (.alpha.R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 133:150348 CA

TITLE: Preparation of alkynyl containing hydroxamic acid compounds as TACE inhibitors

INVENTOR(S): Levin, Jeremy Ian; Venkatesan, Aranapakam Mudumbai; Cole, Derek Cecil; Chen, James Ming; Davis, Jamie Marie; Grosu, George Theodore

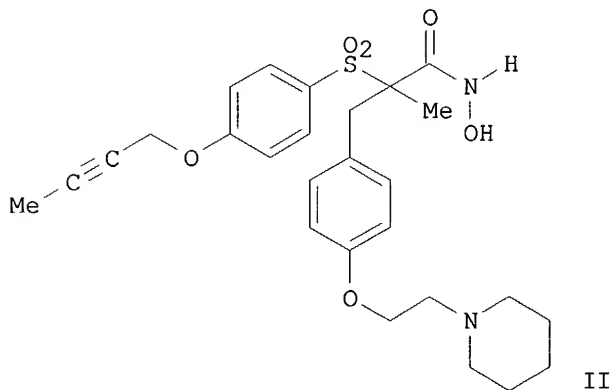
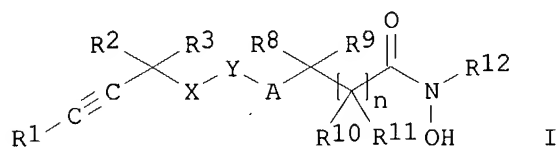
PATENT ASSIGNEE(S): American Cyanamid Company, USA

SOURCE: PCT Int. Appl., 125 pp.

10/055,502

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

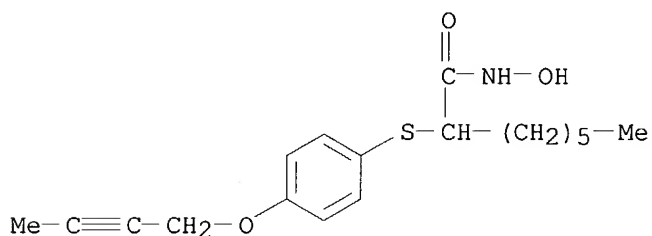
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|-------------------|-----------------|------------|
| WO 2000044713 | A1 | 20000803 | WO 2000-US2078 | 20000127 |
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| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2356346 | AA | 20000803 | CA 2000-2356346 | 20000127 |
| EP 1147080 | A1 | 20011024 | EP 2000-911652 | 20000127 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | |
| BR 2000007783 | A | 20020205 | BR 2000-7783 | 20000127 |
| AU 767754 | B2 | 20031120 | AU 2000-33515 | 20000127 |
| ZA 2001005066 | A | 20020920 | ZA 2001-5066 | 20010620 |
| NO 2001003677 | A | 20010920 | NO 2001-3677 | 20010726 |
| PRIORITY APPLN. INFO.: | | | US 1999-239088 | A 19990127 |
| | | | WO 2000-US2078 | W 20000127 |
| OTHER SOURCE(S): | | MARPAT 133:150348 | | |
| GI | | | | |



AB The title compds. [I; R1 = H, aryl, heteroaryl, etc.; R2, R3 = H, alkyl, CN, CCH; R8-R11 = H, aryl, aralkyl, etc.; R12 = H, aryl, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, S, O, etc.; A = O, S, SO, etc.; X = O, S, SO, etc.; Y = aryl, heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; n = 0-2] and their pharmaceutically acceptable salts, useful in treating disease conditions mediated by TNF-.alpha., such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss, were prepd. E.g., a multi-step synthesis of II.HCl which showed IC50 of 191 nM against TACE, and IC50 of 2 nM, 180 nM, and 200 nM against MMP-1, MMP-9, and MMP-13, resp., was given.

IT **287391-48-4P**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (prepn. of alkynyl contg. hydroxamic acid compds. as TACE inhibitors)

RN 287391-48-4 CA
 CN Octanamide, 2-[[4-(2-butynyloxy)phenyl]thio]-N-hydroxy- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L8 0 L6

=> d his

(FILE 'HOME' ENTERED AT 11:17:46 ON 15 JUN 2004)

FILE 'REGISTRY' ENTERED AT 11:18:47 ON 15 JUN 2004

L1 STRUCTURE UPLOADED
 L2 0 S L1 SAM
 L3 0 S L1 FULL
 L4 STRUCTURE UPLOADED
 L5 5 S L4 SAM
 L6 135 S L4 FULL

FILE 'CA' ENTERED AT 11:20:13 ON 15 JUN 2004

L7 3 S L6

FILE 'CAOLD' ENTERED AT 11:20:28 ON 15 JUN 2004

L8 0 S L6

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10/055,502

---Logging off of STN---

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Executing the logoff script...

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STN INTERNATIONAL LOGOFF AT 11:24:27 ON 15 JUN 2004

18/055,502

Seaman, Margaret**Subject: FW: 502**

* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 10:34:29 ON 15 JUN 2004

=> file reg

Uploading C:\STNEXP4\QUERIES\502.str



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chain bonds :

1-3 1-12 3-4 4-5 5-8 6-8 7-8 7-9 12-14 14-15 15-16

exact/norm bonds :

1-3 1-12 3-4 6-8 7-8 7-9 12-14

exact bonds :

4-5 5-8 14-15 15-16

G1:C,O,S,N

Match level :

1:Atom 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 12:CLASS

14:CLASS 15:CLASS 16:CLASS

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Saturation : Unsaturated

L1 STRUCTURE UPLOADED

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L1 HAS NO ANSWERS

L1 STR

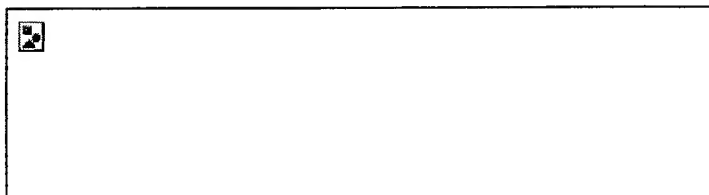


6/15/04

Structure attributes must be viewed using STN Express query preparation.

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L2 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 287392-45-4 REGISTRY
 CN Benzeneacetamide, α -[[4-(2-butynyloxy)phenyl]sulfinyl]-4-ethoxy-N-hydroxy- (9CI) (CA INDEX NAME)
 FS 3D CONCORD
 MF C20 H21 N O5 S
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 DT.CA Caplus document type: Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s l1 full
 L3 135 SEA SSS FUL L1

 => file caplus
 => s l3
 L4 3 L3

 => s l4 and pd<feb 1999
 19589939 PD<FEB 1999
 (PD<19990200)
 L5 0 L4 AND PD<FEB 1999

=> dis l4 1-3 bib abs fhitr

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 2002:66852 CAPLUS Full-text
 DN 136:118280
 TI Preparation of N-hydroxy[(alkynyloxy)phenylsulfanyl]alkanoamides and analogs as TACE and MMP inhibitors
 IN Levin, Jeremy I.; Venkatesan, Aranapakam M.; Cole, Derek C.; Chen, James M.; Davis, Jamie M.; Grosu, George T.
 PA American Cyanamid Company, USA
 SO U.S., 43 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|-----------------|------|----------|-----------------|----------|
| PI | US 6340691 | B1 | 20020122 | US 2000-492977 | 20000127 |
| | US 2002147342 | A1 | 20021010 | US 2001-55502 | 20011113 |
| PRAI | US 1999-160085P | P | 19990127 | | |
| | US 2000-492977 | A3 | 20000127 | | |

OS MARPAT 136:118280

AB R1C.tplbond.CCR2R3Z1Z2Z3CR8R9ZCON(OH)R12 [I; R1 = H, alkyl, (hetero)aryl, etc.; R2,R3 = H, cyano, alkyl, CCH (sic); R8,R9 = H, aryl(alkyl), heteroaryl, etc.; R12 = H, heterocyclyl, (hetero)aryl, etc.; Z = bond, (un)substituted CH2, -CH2CH2; Z1 = O, SOO-2, (un)substituted NH, C (sic); Z2 = (hetero)arylene; Z3 = O, SOO-2, (un)substituted NH, CH (sic)] were prepared Thus, MeCHBrCO2Et was thioetherified by 4-(HO)C6H4SH and the product etherified by MeC.tplbond.CCH2Br to give, in 2 addnl. steps, 4-(MeC.tplbond.CCH2O)C6H4SCHMeCONHOH. Data for biol. activity of I were given.

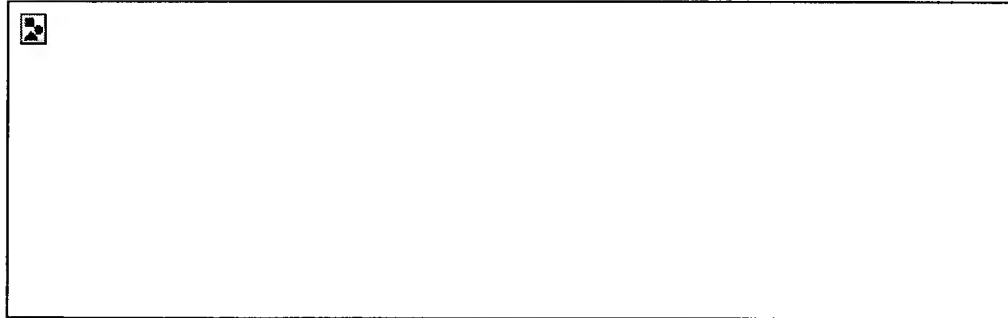
IT 287391-43-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-hydroxy[(alkynyloxy)phenylsulfanyl]alkanoamides and analogs as TACE and MMP inhibitors)

RN 287391-43-9 CAPLUS

CN Benzenepropanamide, α -[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy- α -methyl-4-[2-(1-piperidinyl)ethoxy]-, monohydrochloride (9CI) (CA INDEX NAME)



RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:762982 CAPLUS Full-text

DN 135:318704

TI Preparation of benzimidazole-, benzoxazole- and benzothiazolesulfonamide amino acid derivatives as selective matrix metalloproteinase inhibitors

IN Park, Young-Jun; Bae, Hae-Young; Yoo, Ji-Uk; Chae, Myeong-Yun; Paek, Sang-Hyun; Min, Hye-Kyung; Park, Hyun-Gyu; Ryu, Choon-Ho; Kim, Kyung-Chul; Lee, Jeoung-Wook

PA Samsung Electronics Co., Ltd., S. Korea

SO PCT Int. Appl., 115 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|--|------|----------|-----------------|----------|
| PI | WO 2001077092 | A1 | 20011018 | WO 2001-KR585 | 20010407 |
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| | AU 2001048884 | A5 | 20011023 | AU 2001-48884 | 20010407 |
| | EP 1208092 | A1 | 20020529 | EP 2001-922101 | 20010407 |
| | R: | | | | |
| | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| | JP 2003530389 | T2 | 20031014 | JP 2001-575566 | 20010407 |
| | US 2002169314 | A1 | 20021114 | US 2001-18507 | 20011206 |
| | US 6548667 | B2 | 20030415 | | |
| PRAI | KR 2000-18327 | A | 20000407 | | |
| | KR 2000-18328 | A | 20000407 | | |
| | KR 2000-18431 | A | 20000408 | | |
| | WO 2001-KR585 | W | 20010407 | | |
| OS | MARPAT 135:318704 | | | | |
| GI | | | | | |



AB The present invention provides novel sulfonamide derivs. (I (e.g. (2R)-3-methyl-2-[(2-phenylthiobenzothiazole-6-sulfonyl)amino]butanoic acid Me ester), II (n = 0-4) and III (n = 0-4)), useful as an inhibitors of matrix metalloproteinase (MMP), its isomers, pharmaceutically acceptable salts thereof and a process for preparing the same. Since the sulfonamide derivs. of the present invention selectively inhibit MMP activity in vitro, the MMP inhibitors comprising the sulfonamide derivs. as an effective ingredient can be practically applied for the prevention and treatment of all sorts of diseases caused by overexpression and overactivation of MMP. In I: R1 denotes H, C1-12 alkyl, carbocyclic aryl-lower alkyl, C3-7 cycloalkyl, C3-7 cycloalkyl-lower alkyl, (oxo, amino or thio) C3-7 cycloalkyl, (oxo, amino or

thio) C3-7 cycloalkyl-lower alkyl, C2-12 lower alkenyl, C2-12 lower alkynyl, carbocyclic aryl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, halo lower alkyl, biaryl-lower alkylarylalkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl (thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, (N-lower alkylpiperazino, or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl. R2 denotes H, lower alkyl, carbocyclic aryl-lower alkyl, C1-4 carbocyclic aryl-lower alkyl, C1-4 heterocyclic aryl-lower alkyl, C1-5 alkoxyphenyl-lower alkyl, C1-5 alkenoxyphenyl-lower alkyl, C1-5 alkynoxyphenyl-lower alkyl, heterocyclic aryl-lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, thio-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, carboxy-lower alkyl, (amino, mono or dialkylamino) lower alkyl or acylamino lower alkyl. R3 denotes H or C1-6-lower alkyl. R4 denotes H, C1-12 alkyl, C3-7 cycloalkyl, C3-7 cycloalkyl-lower alkyl, (oxo, amino or thio) C3-7 cycloalkyl, (oxo, amino or thio) C3-7 cycloalkyl-lower alkyl, carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, biaryl-lower alkyl, halo lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, carboxy lower alkyl, (N-lower alkylpiperazino, or N-carbocyclic or heterocyclic aryl piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl. R5 denotes hydroxy, alkoxy, halogen, thiol, thioalkoxy or hydroxylamine. X1 and X2 denote N-R7 (R7 is H, C1-6-lower alkyl, aryl, heteroaryl or arylalkyl), S or O. I can be prepared by (i) reacting a sulfonyl halide with H₂NCR₂R₃CO₂R₆ (R₆ = protecting group) in an organic solvent in the presence of a base to give a sulfonamide; (ii) replacing the H on N using R₄-L (L = reactive leaving group) in an organic solvent in the presence of a base; and (iii) hydrolyzing the intermediate to give I (R₅ = OH), or further condensing I (R₅ = OH) to prepare I (R₅ = NHOH). Alternatively, I can be prepared by (i) chlorosulfonylating IV; (ii) reacting this intermediate with an amino acid derivative in an organic solvent in the presence of base to give a sulfonamide; (iii) heating this intermediate and R₁-X₂H together at 70 to 80° in an organic solvent in the presence of base to cause substitution for C1; (iv) reacting this intermediate with R₄-L (L = reactive leaving group) in an organic solvent in the presence of base to cause substitution for H on N; and, (v) hydrolyzing this intermediate into I (R₅ = OH), or further condensing I (R₅ = OH) to prepare I (R₅ = NHOH). .apprx.70 Example preps. of intermediates and products are given. Inhibition rates for some of the claimed compds. are reported for gelatinase A (MMP-2), gelatinase B (MMP-9) and collagenase (MMP-1).

IT 367517-41-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation of benzimidazole-, benzoxazole- and benzothiazolesulfonamide amino acid derivs. as selective matrix metalloproteinase inhibitors)

RN 367517-41-7 CAPLUS

CN Benzenepropanamide, α -[[[2-(heptylthio)-6-benzothiazolyl]sulfonyl]amino]-N-hydroxy-4-(2-propynyloxy)-, (α R)-
(9CI) (CA INDEX NAME)

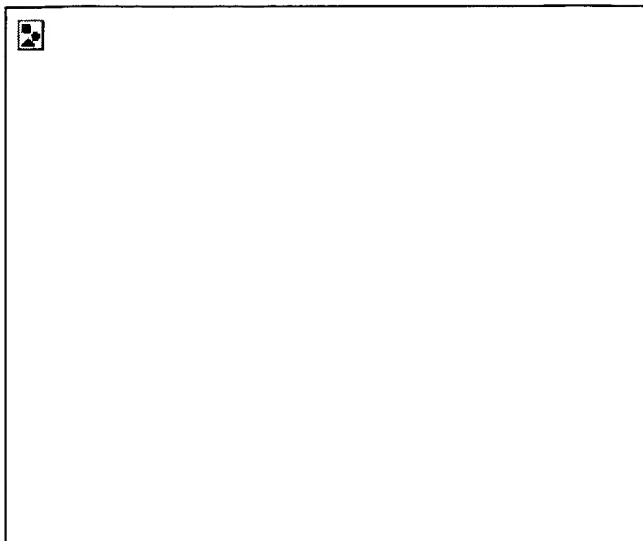
Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:535106 CAPLUS Full-text
DN 133:150348
TI Preparation of alkynyl containing hydroxamic acid compounds as TACE
inhibitors
IN Levin, Jeremy Ian; Venkatesan, Aranapakam Mudumbai; Cole, Derek Cecil;
Chen, James Ming; Davis, Jamie Marie; Grosu, George Theodore
PA American Cyanamid Company, USA
SO PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----------------------|------|----------|--|----------|
| PI WO 2000044713 | A1 | 20000803 | WO 2000-US2078 | 20000127 |
| W: | | | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | |
| RW: | | | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | |
| CA 2356346 | AA | 20000803 | CA 2000-2356346 | 20000127 |
| EP 1147080 | A1 | 20011024 | EP 2000-911652 | 20000127 |
| R: | | | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | |
| BR 2000007783 | A | 20020205 | BR 2000-7783 | 20000127 |
| AU 767754 | B2 | 20031120 | AU 2000-33515 | 20000127 |
| ZA 2001005066 | A | 20020920 | ZA 2001-5066 | 20010620 |
| NO 2001003677 | A | 20010920 | NO 2001-3677 | 20010726 |
| PRAI US 1999-239088 | A | 19990127 | | |
| WO 2000-US2078 | W | 20000127 | | |
| OS MARPAT 133:150348 | | | | |
| GI | | | | |



AB The title compds. [I; R1 = H, aryl, heteroaryl, etc.; R2, R3 = H, alkyl, CN, CCH; R8-R11 = H, aryl, aralkyl, etc.; R12 = H, aryl, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, S, O, etc.; A = O, S, SO, etc.; X = O, S, SO, etc.; Y = aryl, heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; n = 0-2] and their pharmaceutically acceptable salts, useful in treating disease conditions mediated by TNF- α , such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss, were prepared E.g., a multi-step synthesis of II.HCl which showed IC50 of 191 nM against TACE, and IC50 of 2 nM, 180 nM, and 200 nM against MMP-1, MMP-9, and MMP-13, resp., was given.

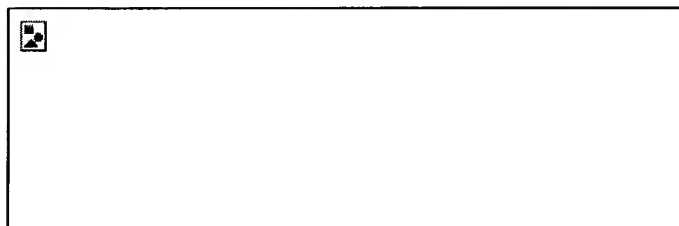
IT **287391-48-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of alkynyl containing hydroxamic acid compds. as TACE inhibitors)

RN 287391-48-4 CAPLUS

CN Octanamide, 2-[[4-(2-butynyloxy)phenyl]thio]-N-hydroxy- (9CI) (CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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